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Seventh Annual Report on

Carcinogens

Summary 1994

U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
Public Health Service

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* For the purpose of this Report, "known carcinogens" are defined as those substances for which the evidence from human studies indicates that there is a causal relationship between exposure to the substance and human cancer.

** For the purpose of this Report, substances "which may reasonably be anticipated to be carcinogens" are defined as those for which there is a limited evidence of carcinogenicity in humans or sufficient evidence of carcinogenicity in experimental animals.

INTRODUCTION

The American public is concerned about cancer and cancer hazards. especially about ways to prevent the occurrence or decrease the incidence of cancers.

Many scientists believe that a significant fraction of all cancers may be associated with the environment in which we live and work. In this context. the environment is understood as "anything that interacts with humans. including substances eaten. drunk. and smoked; natural and medical radiation: workplace exposures; drugs; aspects of sexual behavior; and substances in air. water. and soil (OTA. 1981)." Although we rarely know the environmental factors and conditions which are responsible for the development of specific cancers. in some cases we are beginning to have some understanding. It is the hope of many scientists in these fields that much of the cancer associated with the environment may be avoidable.

Americans. concerned with the relationships between their environment and cancer. have asked for information about substances that cause or might cause cancer.

Section 262 of Public Law 95-622 of November 9. 1978[1] reflects the requests for this information. Section 301 (b) (4) of the Public Health Service Act added by this section stipulates that the Secretary of the Department of Health and Human Services (formerly the Department of Health. Education. and Welfare) shall publish an annual report which contains:

A) a list of all substances (i) which either are known to be carcinogens or may reasonably be anticipated to be carcinogens; and (ii) to which a significant number of persons residing in the United States are exposed;

B) information concerning the nature of such exposure and the estimated number of persons exposed to such substances;

C) a statement identifying (i) each substance contained in the list under subparagraph (A) for which no effluent. ambient. or exposure standard has been established by a Federal agency; and (ii) for each effluent. ambient. or exposure standard established by a Federal agency with respect to a substance contained in the list under subparagraph (A). the extent to which. on the basis of available medical. scientific. or other data. such standard. and the implementation of such standard by the agency. decreases the risk to public health from exposure to the substance; and

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1 Community Mental Health Extension Centers Act of 1978 [Amendments].

D) a description of (i) each request received during the year involved —

(I) from a Federal agency outside the Department of Health, Education, and Welfare for the Secretary, or

(II) from an entity within the Department of Health, Education, and Welfare to any other entity within the Department, to conduct research into, or testing for, the carcinogenicity of substances to provide information described in clause (ii) of Subparagraph (C), and (ii) how the Secretary and each such other entity, respectively, have responded to each request.

Annual Reports on Carcinogens are issued in response to these requirements. These reports discuss individual substances, mixtures of chemicals, or exposures associated with technological processes which are known to be carcinogens or which may reasonably be anticipated to be carcinogens; they contain information received from Federal agencies participating in the preparation of the Reports.

The Annual Reports on Carcinogens are informational documents only; they serve as meaningful compilations of data on the carcinogenicity of the listed substances in humans and/or animals, on the potential for exposure to these substances, and on the regulations promulgated by Federal agencies to limit exposure to them. The Reports represent an initial step in hazard identification of the substances selected for inclusion. The Reports do not present assessments of carcinogenic risk. The listing of a substance in the Annual Report, therefore, does not establish that such substance presents a risk to persons in their daily lives. Such risk assessments are properly the purview of the appropriate Federal, State, and local health regulatory and research agencies.

Participants

Within the Department of Health and Human Services, the responsibility for preparing these Annual Reports has been given to the National Toxicology Program.[2] Agencies participating in this effort through the NTP Working Group for the Annual Reports on Carcinogens are:

Agency for Toxic Substances and Disease Registry (ATSDR)

Centers for Disease Control/National Institute for Occupational Safety and Health (CDC/NIOSH)

Consumer Product Safety Commission (CPSC)

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[2] DHHS member agencies participating in NTP are NIH/NCI; NIH/NIEHS; FDA/National Center for Toxicological Research (FDA/NCTR); CDC/NIOSH; and Agency for Toxic Substances and Disease Registry (ATSDR).

U.S. Environmental Protection Agency (EPA)

Food and Drug Administration (FDA)

National Institutes of Health/National Cancer Institute (NIH/NCI)

National Institutes of Health/National Institute of Environmental Health Science (NIH/NIEHS)
National Institutes of Health/National Library of Medicine (NIH/NLM)

U.S. Department of Labor/Occupational Safety and Health Administration (DOL/OSHA)

Four of these agencies — CPSC, EPA, FDA, and OSHA — are responsible for regulating hazardous substances and limiting the exposure to and use of such substances.

Most of the information in each entry of the Annual Report on Carcinogens on "Use", "Production", and "Exposure" is provided by participants from the regulatory agencies given above.

Identifying Carcinogens

For many years, government research agencies, industries, universities, and other research organizations have studied various substances to ascertain those that might cause cancer. Other Federal agencies have been developing information on possible exposure and potential hazards and making rules and regulations to control substances which have been identified as carcinogens.

Many of the substances, mixtures of chemicals, and occupational exposures associated with technological processes that are listed in the Seventh Annual Report on Carcinogens have been chosen from the "IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans" published by the International Agency for Research on Cancer (IARC) in Lyon, France.[3] Each monograph is the product of an individual working group of experts in chemical carcinogenesis and related fields. The experts evaluate the data for each substance included in a monograph. The evaluation is based on the published information available at the time the working group was convened. Recently (Spring 1991), IARC has released a report of an ad hoc Working Group containing a new updating of all entries in the first 53 volumes of this series. Also described in Supplement 7 are revised evaluation criteria to be used by IARC in

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[3] The IARC address is: 150 cours Albert-Thomas, 69372 Lyon Cedex 08, France. WHO/IARC Publications may be obtained from WHO Publications Centre USA, 49 Sheridan Avenue, Albany, New York 12210.

classification schemes for both human and animal data/experiments on the carcinogens effects of chemicals (IARC S.7, 1987).

Clause (i) in subparagraph (4)(A) of Section 301 (b) of the Public Health Service Act requires "a list of all substances which are either known to be carcinogens or may reasonably be anticipated to be carcinogens." For the purpose of this report, the degree of evidence is as follows:

1) Known to be carcinogens:

   There is sufficient evidence of carcinogenicity from studies in humans which indicates a causal relationship between the agent and human cancer.

2) Reasonably anticipated to be carcinogens:

   A. There is limited evidence of carcinogenicity from studies in humans, which indicates that causal interpretation is credible, but that alternative explanations, such as chance, bias or confounding, could not adequately be excluded, or

   B. There is sufficient evidence of carcinogenicity from studies in experimental animals which indicates that there is an increased incidence of malignant tumors: (a) in multiple species or strains, or (b) in multiple experiments (preferably with different routes of administration or using different dose levels), or (c) to an unusual degree with regard to incidence, site or type of tumor, or age at onset. Additional evidence may be provided by data concerning dose-response effects, as well as information on mutagenicity or chemical structure.

The reader is reminded that the Seventh Annual Report on Carcinogens (and all previous editions) is a condensation of large amounts of data and conclusions made by bodies which peer review the data submitted as evidence about cancer and its relation to specific exposures. As such, the Seventh Annual Report on Carcinogens must be less detailed about the actual tests and their drawbacks. The original monographs on each listing are given in the references, and the reader is advised to turn to these for the specific arguments, both pro and con, which went into the listing decision.

Human and Animal Studies

Both human and animal studies, where available, are used to identify chemicals as possible carcinogens for humans. The strongest evidence for relationships between exposure to any given chemical and cancer in humans comes from carefully conducted epidemiological studies. Good epidemiological studies of cancer must consider the latent period of most cancer development since the exposure to the carcinogen often occurs many years (sometimes 20-30 years or more) before the first sign of cancer appears. As an alternative to what is usually missing in epidemiological studies of suspected carcinogens for humans (accurate information about dose and duration of exposure, and interactions of the suspected carcinogen with other chemicals or modifiers), scientists can use well-designed animal studies. In these, the suspected carcinogen is administered to large numbers of animals in (usually at least) two species over a range of doses and times with all parameters chosen to maximize the possibility of producing cancer (e.g., the doses of suspected carcinogen are usually large).

It is not possible to predict perfectly what will be a carcinogen in humans from animal tests alone, but most errors are becoming better understood, and it is true that most human carcinogens do produce cancers in animals, when these chemicals are adequately tested. Experimental carcinogenesis research is based on the premise that chemicals that produce cancer in animals will have similar effects on human cells. Strict correspondence of results in humans with those in animals with any adverse response to chemicals (of which cancer is only one) is not often obtained, but animals remain as the best testing tool we now have for detecting potential hazards of all kinds (OTA, 1981; IARC S.2, 1980).

Relationship of the Annual Report Criteria to IARC Criteria

As noted above, many of the substances listed herein are also listed in the "IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans." In order to understand the relationship between the IARC carcinogen-classification scheme and the Annual Report's classification scheme, it is helpful to compare the two.

The 1988 IARC carcinogen-classification scheme in place at the time that work on the Seventh Annual Report began has four categories. The degree of evidence required for each IARC category is as follows:

Group 1: <u>The agent is carcinogenic to humans</u>

Sufficient evidence of carcinogenicity to humans is necessary. Sufficient evidence is considered by IARC to be evidence that a causal relationship has been established between exposure to the agent and human cancer.

Group 2A: <u>The agent is probably carcinogenic to humans</u>

This category generally includes agents for which there is limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals. On occasion, IARC may classify an agent in this category solely on the basis of limited evidence of carcinogenicity in humans or of sufficient evidence of carcinogenicity in experimental animals in view of supporting evidence from other relevant data.

Group 2B: The agent is possibly carcinogenic to humans

This category generally includes agents for which there is limited evidence in humans in the absence of sufficient evidence in experimental animals. It may also be used when there is inadequate evidence of carcinogenicity in humans or when human data are nonexistent but there is sufficient evidence of carcinogenicity in experimental animals. In some instances, agents may be included for which there is inadequate evidence or no data in humans but limited evidence of carcinogenicity in experimental animals together with supporting evidence from other relevant data.

Group 3: The agent is not classifiable as to its carcinogenicity to humans

Agents are placed in this category when they do not fall into any other group.

Group 4: The agent is probably not carcinogenic to humans

For agents in this category, there is evidence suggesting lack of carcinogenicity in humans together with evidence suggesting lack of carcinogenicity in experimental animals. In some circumstances, agents for which there is inadequate evidence of or no data on carcinogenicity in humans but evidence suggesting lack of carcinogenicity in experimental animals, consistently and strongly supported by a broad range of other relevant data, may be classified in this group.

For experimental-animal data, IARC defines sufficient evidence as evidence that a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) in two or more independent studies in one species carried out at different times or in different laboratories or under different protocols. For further detail on the definitions of degrees of evidence, see IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Man-Made Mineral Fibers and Radon, 1988, Vol. 43.

The Annual Report has necessarily used the statutory language for its two-category carcinogen-classification scheme (as specified in Section 301(b)(4) of the Public Health Service Act). Although the IARC and the Annual Report's schemes do not exactly correspond to one another, the Annual Report's scheme and associated degrees of evidence are based on IARC's classification scheme and degrees of evidence.

The Annual Report's "Reasonably Anticipated" category does not distinguish whether the degree of evidence supporting a given listing corresponds to the IARC categories of either "Probable" or "Possible" carcinogens. The text entries for listed substances, however, make clear whether the degree of evidence supporting the listing corresponds either to the "Probable" or to the "Possible" IARC category.

Inclusion of Substances

The Seventh Annual Report contains most of the substances, groups of substances, and some of the technological processes that were listed in the Sixth Annual Report. Most of these previously included entries have been updated to reflect more current information. Some of the entries found in earlier reports have been altered/removed in this Seventh Annual Report for reasons listed below (see page 13). The Seventh Annual Report presents information on 7 additional substances. Each has been chosen either from substances tested by the NCI Carcinogenesis Testing Program or the National Toxicology Program (NTP); from designations of the participating agencies; or from substances evaluated by the IARC Working Groups. Other substances from the same sources will be added to subsequent Annual Reports.

Section IIA lists all the substances and technological processes included in the Seventh Annual Report. The list is divided into two sublists. One contains substances, groups of substances, or technological processes known to be carcinogens (26 entries). The other sublist of 154 entries includes substances or groups of substances which may reasonably be anticipated to be carcinogens.

Section IIC contains a brief description of each substance or mixture of chemicals, or medical treatment, together with a summary of evidence for its carcinogenicity. References to the original papers on experimental or epidemiological studies, which can be found in the IARC Monographs or in the NCI and NTP bioassay reports, have not always been included in the Seventh Annual Report. Descriptions of two occupational exposures associated with a technological process are also included: coke oven emissions and soots, tars, and mineral oils. The specific carcinogens in these exposures have not been precisely determined.

A substance not listed in this Annual Report may still be a known carcinogen or reasonably anticipated to be a carcinogen.More substances than those included may potentially present a carcinogenic risk to persons living in the United States. These substances will be incorporated into subsequent Annual Reports as data become available. Some chemicals will be included as a result of testing performed by industry in response to EPA's requests under the Toxic Substances Control Act. The National Toxicology Program also will provide new information for these Reports as further test results become available.

The Seventh Annual Report on Carcinogens contains entries on the carcinogenicity of seven metals (arsenic, beryllium, cadmium, chromium, lead, nickel, and thorium). The entries for the individual metals identify those compounds of the metal (and, where appropriate, the elemental metal itself) for which evidence of carcinogenicity in environmentally-exposed humans or experimental animals is sufficient. Relatively few of the many different forms (elemental, salts, complexes, chelates, etc.) of the metals have been fully evaluated for carcinogenicity. The various factors that can influence the carcinogenic potential of a given metal form that should be considered include:

route of exposure, absorption, distribution, valance state, metabolism, elimination, as well as potential for specific biochemical interactions in cells. However, in the absence of specific information a metal shown to be carcinogenic in one of its forms should be considered as being potentially carcinogenic in its other forms.

Ionizing radiation, ultraviolet radiation (including sunlight), tobacco, alcoholic beverages, and some viruses are known or suspected carcinogens. They have not been included in this Report (unless acting in conjunction with a chemical) because ionizing radiation is discussed thoroughly in a General Accounting Office Report, and a Surgeon General's Report reviews the overwhelming relationship between tobacco and cancer (GAO, 1981; OSH, 1982). Several publications issued by the National Cancer Institute explain the relationship of alcoholic beverages, ultraviolet radiation, and viruses to cancer (e.g., Shimkin, 1980).

Certain manufacturing processes, occupations, and mixtures of chemicals have been considered by the International Agency for Research on Cancer (IARC) and have been classified by IARC as sources which are associated with increased incidences of cancer in workers in these settings. Among these are:

1. Boot and Shoe Manufacture and Repair (IARC S.4, 1982; IARC V.25, 1981)

2. Certain Combined Chemotherapy for Lymphomas (IARC S.4, 1982; IARC V.25, 1981)

3. Furniture Manufacture (IARC S.4, 1982; IARC V.1, 1972)

4. Hematite Underground Mining (IARC S.4, 1982; IARC V.1, 1972)

5. Isopropyl Alcohol Manufacturing (Strong-Acid Process) (IARC S.4, 1982; IARC V.15, 1977)

6. Manufacture of Auramine (IARC S-4, 1982; IARC V.1, 1972)

7. Nickel Refining (IARC S.4, 1982; IARC V.2, 1973; IARC V.11,1976)

8. Rubber Industry (IARC S.4, 1982; IARC V.28, 1982)

9. Aluminum Production (IARC 34, 1984; IARC S.7, 1987)

10. Painter (Occupational Exposure as a) (IARC 47, 1989).

The IARC reports dealing with these processes and mixtures are given in the references at the end of this Introduction, and the interested reader is referred to these documents for details. The Seventh Annual Report on Carcinogens does not list these processes/industries/exposures separately since, in most cases, neither the specific substance nor the specific steps in the manufacturing processes that are likely to cause the cancers have been identified. Further, IARC has recognized that many manufacturing processes vary significantly from one country and from one time to another, and the likelihood of variation is great in exposures to whatever causes the observed cancers.

Preparation of the Annual Reports on Carcinogens

The process used to prepare the Annual Reports on Carcinogens involves multiple levels of review, both of the substances considered for inclusion in the Reports and of the completed Reports prior to publication. Continuing opportunities for public comment and participation are also an integral part of the process.

Two Federal scientific review groups evaluate the substances that are potential candidates for inclusion in the Annual Reports on Carcinogens. Each group reviews available data relevant both to the carcinogenicity of the substances and to exposure to the substances of persons residing in the United States.

The first group is the NIEHS Scientific Review Committee.This Committee proposes a list of candidate substances based upon its evaluation of the IARC Monographs, the NTP Technical Reports, and other peer-reviewed carcinogenesis studies. The Committee places emphasis upon the carcinogenicity and related toxicological data, but also reviews information on exposure provided in the study reports and monographs. The list of substances proposed by the Committee for addition to the Report is divided into two sections — those substances known to be carcinogens and those substances reasonably anticipated to be carcinogens.

The second group is the Working Group for the Annual Reports on Carcinogens, which is a Subcommittee of the NTP Executive Committee. Scientists from the following agencies are members of the Working Group: ATSDR, CPSC, EPA, FDA, NCI, NIEHS, NIOSH, NLM, OSHA, and NTP. The Working Group evaluates the list of candidate substances and accompanying data from the NIEHS Scientific Review Committee, as well as two-to-three-page production/use/exposure profiles on each of the substances. These profiles contain data on domestic manufacture and importation, use, and worker exposure which have been retrieved from standard reference sources and available on-line data bases. The Working Group also reviews the data on exposure in the Technical Reports of the NTP carcinogenesis studies and the IARC Monographs, where applicable, as well as information submitted by the members from Agency databases. The Working Group evaluates the exposure data on the candidate substances on a case-by-case basis and develops a list of substances proposed for inclusion in the succeeding Report.

This list of proposed substances with key references is then published in the Federal Register for comment. Final decisions on the substances to be included in the Annual Report and on other issues raised are made after the two review groups have evaluated the submitted comments on each of the issues.

Those comments that recommend that substances be added to the given Annual Report are deferred from consideration by the two review committees until they evaluate candidate substances for the next Annual Report. This enables the public to have the same opportunity for notice and comment on the substances proposed by outside parties as it has on the substances proposed by the review committees for inclusion in the Report.

Once decisions have been made on the chemicals to be included in the Annual Report, the support contractor prepares the initial draft of the Report, which contains an entry on each of the substances judged to be known carcinogens or reasonably anticipated to be carcinogens. As mandated by Congress, these entries include data on the nature of exposure to the substances and the estimated numbers of persons exposed, and information on the Federal regulations promulgated on the substances; in addition, they contain summaries of the relevant carcinogenicity data. The information on Federal regulations and other Federal activities is supplied by the agencies that serve on the Working Group for the Annual Report on Carcinogens. These agencies also contribute data on levels of exposure to the substances under the use situations for which they have jurisdiction.

Following extensive review by NIEHS scientific staff, the draft Report is revised and submitted first to the Working Group for the Annual Reports on Carcinogens and then to the NTP Executive Committee for evaluation. Modifications suggested by member Agencies are incorporated into the document which is then transmitted to the Secretary, Department of Health and Human Services, for final review, approval, and publication.

Substances included in Annual Reports may be delisted from subsequent Reports for one of two reasons. Either exposure to persons residing in the United States can no longer be demonstrated, or there has been a revision in the ruling/findings as to the carcinogenicity of these entries. Chemical substances delisted from Annual Reports are included in Section IIB of subsequent Reports along with the reason for delisting.

A mechanism exists for delisting substances from the Annual Reports which is part of the ongoing review process. Proposals for delisting substances from the reports are first submitted to the NIEHS Scientific Review Committee, which evaluates the data and makes recommendations. The proposals and the Committee recommendations are then submitted to the Working Group for further review. If the Working Group concludes that delisting is warranted, then this proposed change is published in the Federal Register with a request for comments. At subsequent meetings of the NIEHS Scientific Review Committee and of the Working Group, the proposed change is further evaluated, and a decision is made on whether to delist the substance.

Outside requests for delisting substances from a given Annual Report must be received before the two review committees have developed proposed actions relevant to that report, in order for those requests to be considered as part of the review process for that particular Report. Requests received after the committees have developed and published proposals are considered as part of the process for the next Annual Report.

Estimating Exposure

According to clause (ii) of subparagraph (4)(A), this Report is required to include those substances "to which a significant number of people residing in the United States are exposed." Substances to which very few people are exposed are not included for the most part. Some substances that have been banned or restricted in use are contained in the Report (e.g., safrole, arsenical pesticides, mirex), either because people who were previously exposed remain potentially at risk or because these substances are still present in the environment.

Subparagraph (4) (B) requires that the Annual Reports provide "information concerning the nature of such exposure and the estimated number of persons exposed to such substances." The determination of the number of people potentially exposed and the route, intensity, and duration of such exposure for each substance remains a formidable task. This Report attempts to respond to these questions, and wherever adequate answers could be obtained, they are included in Sections IIC and IID.

The National Occupational Hazard Survey (NOHS), conducted by CDC/NIOSH from 1972 to 1974, gave information on the number of workers potentially exposed and on some broader aspects of potential occupational exposure. The National Occupational Exposure Survey (NOES) (1981-1983), has yielded more recent potential exposure data on many of these compounds. Where available, NOES estimates are provided in the profiles on the substances; NOHS figures are also given in some profiles.

Regulatory Status

Subparagraph (4) (C) of Section 301 also requires "a statement identifying (i) each substance contained in the list under subparagraph (A) for which no effluent, ambient, or exposure standard has been established by a Federal agency; ... " The Seventh Annual Report responds to this requirement by appending to the description of each substance a summary of Federal regulations as submitted by the participating agencies.[4] Some of these standards and regulations have been enacted for reasons other than the carcinogenicity of the

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[4] Throughout these volumes recommendations of the National Institute for occupational Safety and Health (NIOSH) are included in the tables of regulations. While NIOSH is not a regulatory agency, the NIOSH findings are often used for the formulation of regulatory actions.

substance; for instance, to prevent other adverse health effects or to improve the quality of the environment or food. Solid or liquid wastes or wastes discharged into the air may contain carcinogens, yet these may be regulated as toxic substances or hazardous pollutants and not specifically as carcinogens. If these regulations reduce exposure to carcinogens, then the cancer risk posed by such substances also will decrease.

Estimating Risk Reduction

Clause (ii) in subparagraph (4)(C) requires a statement identifying "for each effluent, ambient, or exposure standard established by a Federal agency with respect to a substance contained in the list under subparagraph (A), the extent to which, on the basis of available medical, scientific, or other data, such standard, and the implementation of such standard by the agency, decreases the risk to public health from exposure to the substance..." This requires quantified information on the amount of protection from cancer that the public receives from established Federal standards.

Estimating the amount of health protection is perhaps the most difficult task in preparing the Annual Reports. One reason is that most Federal laws concerned with reducing cancer risk have been enacted only within the last 15 years. Given the long period between the initial exposure to a carcinogen and the onset of disease, it is still too early to evaluate to what extent Federal standards and other regulations have decreased the human cancer risk. Another reason is that information on past exposure levels, which could serve as a baseline for estimating future risk reduction, often is not available or accurate.

The risk—the probability of developing cancer—depends on many things, including the intensity, route, and duration of exposure to a carcinogen. Individuals may respond differently to similar exposures, depending on host factors such as age, sex, nutritional status, overall health, and inherited characteristics. Only in a few instances, where studies of long-term human exposures and cancer incidence in restricted environments are available, can risk be estimated with any confidence.

The regulation of asbestos in the workplace provides a good example. In 1969, under the Walsh-Healey Act, which then regulated only firms with government contracts, the standard for permissible exposure was 12 fibers of asbestos per cubic centimeter (cm3) of air. Under the Occupational Safety and Health Act, this standard was reduced to 5 fibers/cm3 in 1972 and to 2 fibers/cm3 in 1976. On April 17, 1980, a joint NIOSH/OSHA Working Group recommended the elimination of all nonessential uses of asbestos and the implementation of a public health program to reduce human exposures. On April 10, 1984, OSHA proposed a rule lowering the permissible exposure to 0.2 or 0.5 fibers/cm3 (5 pm in length) and requiring other provisions for employee protection. The high risk in workers exposed before 1969 is well known. The actual data on exposure levels in the 1940s, 1950s, and 1960s are fragmentary, although exposure levels were certainly unacceptably high by today's standards. The incidence of mesotheliomas and lung cancer has been shown to be causally related to asbestos exposure. However, such malignancies generally develop 20-40 years after first exposure to asbestos. For these reasons, we will not know until early in the next century to what extent the series of exposure reductions in the 1970s and 1980s have reduced the cancer risk in persons exposed to asbestos.

One possible way to provide quantitative estimates of risk reduction might be to assume that the cancer risk is directly proportional to exposure. This approach also supposes that data on past and present exposure levels are available, or that conditions in all workplaces are in compliance with regulations. However, information supporting these assumptions is only rarely obtainable. Nevertheless, it is reasonable and prudent to accept that the reduction of exposure, for any reason, particularly to substances shown to be carcinogenic in experimental animals, will decrease the incidence of cancer. This is the basis of current regulatory policies that aim to lower human exposure to cancer-causing substances and thereby improve public health. For a more detailed discussion of some of the issues involved, see the previously cited report to Congress on the assessment of technologies for determining cancer risks from the environment (OTA, 1981).

Requests for Research, Testing, and Information

The last requirement of subparagraph (4)(D) is:

a description of (i) each request received during the year involved—

(I) from a Federal agency outside the Department of Health, Education, and Welfare for the Secretary, or

(II) from an entity within the Department of Health, Education, and Welfare to any other entity within the Department, to conduct research into, or testing for, the carcinogenicity of substances or to provide information described in clause (ii) of subparagraph (C), and (ii) how the Secretary and each such other entity, respectively, have responded to each such request."

Section III of the Report includes tables listing such requests as received from the participating agencies. The inclusion of a substance in these tables does not imply that it is a known or reasonably anticipated carcinogen.

Other Information

Section IV is a glossary of terms, acronyms, and units of measurement used frequently in the Seventh Annual Report.Section V is a list of Chemical Abstracts Service (CAS) registry numbers of chemical substances in this Report, and the page number where a profile of the substance appears in the Seventh Annual Report. Section VI is a list of participating agencies and their representatives who collaborated in preparing the Seventh Annual Report. Section VII contains a cumulative list of Federal Regulations and Federal Register citations for this report.

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drugs for mild-to-moderate pain associated with the musculoskeletal system. Such mixtures have been used for more than 80 years (IARC V.13, 1977).

PRODUCTION

FDA reported that analgesic mixtures containing phenacetin are not currently manufactured in or imported into the United States. No data on historical production, imports, or exports were available.

EXPOSURE

The primary routes of potential human exposure to analgesic mixtures containing phenacetin are ingestion, inhalation, and dermal contact. Potential consumer exposure could have occurred through ingestion of analgesic mixtures containing phenacetin as pharmaceuticals. Mixtures with phenacetin usually contained 150-200 mg phenacetin (IARC V.13, 1977). Potential occupational exposure could have occurred through inhalation and dermal contact for workers involved in manufacturing, formulating, packaging, or administering the pharmaceuticals.

REGULATIONS

Analgesic mixtures containing phenacetin are not regulated by EPA because they were used as pharmaceuticals and in low quantities relative to other chemicals. However, there may be a small pollution problem relative to hospital wastes.

FDA regulates these mixtures under the Food, Drug, and Cosmetic Act (FD&CA) as prescription drugs. FDA has withdrawn approval of all drugs containing phenacetin and has required manufacturers to reformulate the mixtures to omit phenacetin. OSHA regulates analgesic mixtures containing phenacetin under the Hazard Communication Standard and as chemical hazards in laboratories.

ARSENIC AND CERTAIN ARSENIC COMPOUNDS

CARCINOGENICITY

There is limited evidence for the carcinogenicity of arsenic (CAS No. 7440-38-2) and the following arsenic compounds in experimental animals: arsenic pentoxide (1303-28-2), arsenic trioxide (1327-53-3), calcium arsenate (7778-44-1), calcium arsenite (1:1) (52740-16-6), calcium arsenite (2:1) (15194-98-6), calcium arsenite (2:3) (27152-57-4), disodium hydrogen arsenate (10048-95-0), lead arsenate (7784-40-9), potassium arsenate (7784-41-0), potassium arsenite (13464-35-2), sodium arsenate (7631-89-2), and sodium arsenite (7784-46-5) (IARC V.2, 1973; IARC V.23, 1980; IARC S.4, 1982; IARC S.7, 1987). When injected subcutaneously during the first 3 days of life into mice whose mothers had been injected subcutaneously once during gestation, arsenic trioxide induced lung adenomas. When administered by intratracheal instillation, arsenic trioxide induced low incidences of carcinomas, adenomas, papillomas and adenomatoid lesions of the respiratory tract in hamsters of both sexes. It induced a low incidence of adenocarcinomas at the site of its implantation into the stomach of rats.

There is no separate CAS registry number assigned to these mixtures. Phenacetin is included separately in the Annual Report on Carcinogens, p. 698.

A high incidence of lung carcinomas was induced in rats after a single intratracheal instillation of a pesticide mixture containing calcium arsenate. Intratracheal instillations of calcium arsenate into male hamsters resulted in a borderline increase in the incidence of lung adenomas, whereas no such effect was observed with arsenic trisulfide. When administered in the drinking water, sodium arsenite enhanced the incidence of renal tumors induced in male rats by intraperitoneal injection of N-nitrosodiethylamine.

An IARC Working Group reported that there is sufficient evidence for the carcinogenicity of inorganic arsenic compounds in humans (IARC S.7, 1987). (See the Introduction, p. viii, for a discussion on the carcinogenicity of metals.) Many cases of skin cancer have been reported among people exposed to arsenic through medical treatment with inorganic trivalent arsenic compounds. In some instances, skin cancers have occurred in combination with other cancers, such as liver angiosarcoma, intestinal, and urinary bladder cancers and meningioma. Epidemiological studies of cancer after medical treatment with arsenic have shown an excess of skin cancers, but no clear association with other cancers has been obtained. No relation was found between prostatic cancer and treatment of syphilis with arsenicals. An association between environmental exposure to arsenic through drinking water and skin cancer has been observed and confirmed. Epidemiological studies in areas where drinking water contained 0.35-1.14 mg/l arsenic elevated risks for cancers of the bladder, kidney, skin, liver, lung, and colon in both men and women. Occupational exposure to inorganic arsenic, especially in mining and copper smelting, has quite consistently been associated with an increased risk of cancer. An almost tenfold increase in the incidence of lung cancer was found in workers most heavily exposed to arsenic, and relatively clear dose-response relationships have been obtained with regard to cumulative exposure. Other smelter worker populations have been shown to have consistent increases in lung cancer incidence, as well as increases of about 20% in the incidence of gastrointestinal cancer and of 30% for renal cancer and haematolymphatic malignancies. The observation in an earlier study of an increase in lung risk among a population of smelter workers has been confirmed, with a risk of sixfold to eightfold among roasters. With regard to histological type of lung cancer, a significant, relative excess of adenocarcinomas and a slight excess of oat cell cancers were seen among smelter workers.

PROPERTIES

Arsenic and certain arsenic compounds occur in crystalline, powder, amorphous, or vitreous forms. Elemental arsenic is not soluble in water; calcium arsenate, and calcium arsenites (1:1), (2:1), and (2:3) are sparingly soluble in water; the remaining arsenicals are soluble in water. Arsenic pentoxide, potassium arsenite, and the three sodium salts are soluble in ethanol. Arsenic, arsenic pentoxide, arsenic trioxide, the calcium arsenites, lead arsenate, and potassium arsenate are soluble in various acids. When heated to decomposition, arsenic compounds emit toxic arsenic fumes.

Arsenic is available in a technical grade (99% pure) and in a high-purity grade (99.999+% pure) which is intended for semiconductor use. Arsenic pentoxide, sodium arsenite, sodium arsenate, potassium arsenate, and potassium arsenite are available in technical and chemically pure grades. Potassium arsenite is also available in a 1% aqueous solution commonly known as Fowler's solution. Arsenic trioxide can be purchased in a 95% crude grade, in a 99% pure refined grade, as a 1% solution in approximately 5% hydrochloric acid, in 2-mg tablets, and as a paste. Calcium arsenate is available as pure grade with 99% purity or as a grade containing 61% calcium arsenate, 9% calcium arsenite, and an excess of lime and calcium carbonate. Lead arsenate is available as acid lead arsenate containing 33% arsenic pentoxide, as a wettable powder (94-98% pure), as a dust, and as a paste.

USE

The estimated end-use distribution of arsenic in 1990 was 70% in wood preservatives, 22% in agricultural chemicals (principally herbicides and desiccants), 4% in glass, 2% in nonferrous alloys and 2% in other uses (USDOI, 1991). Metallic arsenic was used in nonferrous alloys and in the electronics industry for semiconductor materials. Arsenic pentoxide, calcium arsenate, lead arsenate, and sodium arsenate are used in the formulation of wood preservatives. There is an increased use of arsenic trioxide by the wood preservative industry due to its use in formulating chromated copper arsenate (USDOI, 1987). Calcium arsenate is used as an insecticide on cotton and against certain soil insects, as an herbicide for treating turf and lawns to control weeds, and as a pesticide on fruits and vegetables. Sodium arsenate is used in ant killers and in animal dips as an insecticide. Sodium arsenite is used in low percentages in herbicides for ant control and weed control, for destroying trees and stumps, in animal dips, in pesticide baits, and for soil treatment against termites. Although there is no present commercial use for calcium arsenite (1:1), it was formerly used as an insecticide, pesticide, and molluscicide. Lead arsenate was originally a part of insecticide formulations, though this use is currently negligible. Arsenic, arsenic trioxide, lead arsenate, and potassium arsenite are used in various medicines, mostly veterinary. Formerly, disodium hydrogen arsenate was also used in this capacity. Potassium arsenite as Fowler's solution is a hematinic used as a temporary medication for the treatment of myelogenous leukemia and certain skin lesions. The use of Fowler's solution as a veterinary medicine is not generally deemed acceptable for widespread use. Arsenic (including metallic arsenic), arsenic pentoxide, and arsenic trioxide are used as alloying additives, particularly with lead and copper. Arsenic and arsenic trioxide are also used in the manufacture of low-melting glasses. High-purity arsenic metal is used in the electronics industry for semiconductor materials. There is no present commercial use for potassium arsenate, although it has been used in fly baits, hide preservation, and textile printing and as a lab reagent. Arsenic trioxide is the source for 97% of all arsenic products (IARC V.2, 1973; IARC V.23, 1980).

PRODUCTION

In 1990, the United States imported over 1.7 million lb of arsenic metal and 61.7 million lb of arsenic trioxide (USDOI, 1991). Arsenic trioxide was imported and then converted to arsenic acid by three major companies, one headquartered in the United States and two headquartered in the United Kingdom. In 1989, the United States imported 2.6 million lb of arsenic metal and 66 million lb of arsenic trioxide (USDOI, 1990). The United States imported approximately 1.3 million lb of arsenic metal and 61.7 million lb of arsenic trioxide. In 1985, the sole domestic producer of arsenic ceased operation, resulting in the United States becoming completely dependent upon foreign suppliers. This dependency is anticipated to continue indefinitely (USDOI, 1988). Since the sole producer of arsenic ceased operation in 1985, permission to publish data, previously considered proprietary, was given to the Bureau of Mines in 1986. In 1987, it was estimated that 1.38 million lb of arsenic metal and 59 million lb of arsenic trioxide were imported. Imports of arsenic metal in 1986 were reported to be 870,000 lb, and 56.6 million lb of arsenic trioxide were imported. In 1985, the final year of production, 4.8 million lb of arsenic, reported as arsenic trioxide containing 76% arsenic by weight, were produced, while 895,000 lb of arsenic metal and 36.2 million lb of arsenic trioxide were imported. In 1984, 14.9 million lb of arsenic were produced, and 670,205 lb of arsenic metal and 30.8 million lb of arsenic trioxide were imported. Domestic production of arsenic in 1983 was 16.1 million lb. In 1983, 535,723 lb of arsenic metal and 22.5 million lb of arsenic trioxide imported. In 1982, 17.6 million lb of arsenic were produced, and 299,828 lb of arsenic metal and 32.2 million lb of arsenic trioxide were imported (USDOI, 1988; USDOI, 1987). The 1979 TSCA Inventory reported that in 1977, there were nine producers of arsenic with a total production volume of 1.65 million lb and five firms imported 614,000 lb. The CBI Aggregate was between 1 and 100 million lb (TSCA, 1979).

Four companies, three utilizing imported material, produced arsenic acid (USDOI, 1990). There are single producers of calcium arsenate and potassium arsenate, two producers of lead arsenate, and four producers of sodium arsenite, with no reported production volumes. Production of potassium arsenite is believed to be limited to a very small quantity produced by a few companies (IARC V.23, 1980). The Bureau of Mines has reported the amount of arsenic compounds imported and exported for the years covering 1982 through 1989. References to arsenic compounds include arsenic acid, sodium arsenate, lead arsenate, and miscellaneous compounds. In 1989, the United States imported 132,000 lb of arsenic acid (USDOI, 1990). Imports of arsenic compounds for 1988 were 2.3 million lb and 880,000 lb were exported. In 1987, the United States imported an estimated 5.1 million lb and exported an estimated 176,369 lb of arsenic compounds. In 1986, imports of arsenic compounds were 3.2 million lb and exports were 478,403 lb. In 1985, 4.9 million lb of arsenic compounds were imported and 348,330 lb were exported (USDOI, 1988; USDOI, 1987). In 1985, 3.6 million lb of arsenic trioxide or arsenious acid, 358,100 lb of lead arsenate, and 51,117 lb of miscellaneous arsenic compounds were imported (USDOC Imports, 1986). In addition, 5,464 lb of miscellaneous arsenic compounds were exported in 1985 (USDOC Exports, 1986). In 1984, 3.1 million lb of arsenic trioxide or arsenious acid. 160,117 lb of lead arsenate, and 77,686 lb of miscellaneous arsenic compounds were imported (USDOC Imports, 1985). In 1984, 5.8 million lb of arsenic compounds were imported and 167,551 lb were exported. In 1983, imports of arsenic compounds were 7.8 million lb and exports were 187,393 lb. The United States imported 3.8 million lb and exported 5.9 million lb of arsenic compounds in 1982 (USDOI, 1988; USDOI, 1987).

EXPOSURE

The primary routes of potential human exposure to arsenic and certain arsenic compounds are inhalation, ingestion, and dermal contact. NIOSH estimated that 1.5 million industrial workers are potentially exposed to arsenic and its compounds during manufacturing and processing operations. The National Occupational Exposure Survey (1981-1983) indicated that 36,194 total workers, including 4,007 women, are potentially occupationally exposed to arsenic, arsenic pentoxide, arsenic trioxide, or sodium arsenite (NIOSH, 1984). Higher than average worker exposure may occur during the smelting of ores containing arsenic, during pesticide application, and wood preservation (NIOSHb, 1979). ACGIH has adopted a threshold limit value (TLV) of 0.2 mg/m^3 for arsenic and soluble compounds, as arsenic, as an 8-hr time-weighted average (TWA) (ACGIH, 1986). Recent reductions in emissions and improved industrial hygiene practices have substantially reduced occupational exposures (ATSDR, 1989a). Direct consumer exposure to arsenic and arsenic compounds may occur through consumption of foods. Food provides an intake of about 20-70 μg of arsenic per person per day (ATSDR, 1989a). Trace levels of arsenic have been reported in the tissue of livestock that were administered arsenic drugs and feed additives. Potential consumer exposure to arsenic also occurs through the consumption of drinking water contaminated with arsenical pesticides, natural mineral deposits, or improperly disposed arsenical chemicals. EPA has established interim regulations to minimize exposure risks. Additionally, the general population is potentially exposed to arsenic compounds through air emissions from pesticide manufacturing facilities, smelters, cotton gins, glass manufacturing operations, cigarette tobacco, burning of fossil fuels, and other sources. Exposure may also result from natural mineral deposits containing large quantities of arsenic which may result in elevated levels of arsenic in drinking water (ATSDR, 1989a). The Toxic Chemical Release Inventory (EPA) listed 72 industrial facilities that produced, processed, or otherwise used arsenic in 1988 (TRI, 1990). In compliance with the Community Right-to-Know Program, the facilities reported releases of arsenic to the environment which were estimated to total 192,000 lb. The use of topical arsenic medications may also potentially expose a limited portion of the population to arsenic and arsenic compounds.

REGULATIONS

CPSC will monitor the results of the EPA-proposed registration amendments and the voluntary awareness program notifying consumers of hazards associated with exposure to wood treated with arsenic. CPSC is planning no action at present, pending an evaluation of the effectiveness of the these measures. CPSC determined that arsenic, arsenic trioxide, and arsenic compounds were not present in consumer products under CPSC jurisdiction. Subsequently, CPSC requested public comment to verify the accuracy of this information. EPA regulates arsenic and certain arsenic compounds under the Clean Air Act (CAA), Clean Water Act (CWA), Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), Food, Drug, and Cosmetic Act (FD&CA), Resource Conservation and Recovery Act (RCRA), Safe Drinking Water Act (SDWA), and Superfund Amendments and Reauthorization Act (SARA). Arsenic emissions from smelters and other facilities are regulated under CAA. CWA has established effluent guidelines controlling the environmental release of arsenic compounds for certain industrial categories. Reportable quantities (RQs) have been established under CERCLA and CWA for arsenic and certain arsenic compounds. EPA has issued a Rebuttable Presumption Against Registration (RPAR) for eleven inorganic arsenic pesticide products under FIFRA. Tolerances for residues of arsenical pesticides have been established under FD&CA. Under RCRA, EPA regulates arsenic as a hazardous constituent of waste. SDWA limits arsenic in drinking water to a maximum level of 0.05 mg/l. SARA has established threshold planning quantities for some arsenic compounds and subjects arsenic and arsenic compounds to reporting requirements. FDA enforces tolerances set by EPA under FD&CA for residues of pesticides containing arsenic in fruits and vegetables, field crops, and livestock. FDA has also set tolerance limits for the residue of arsenic compounds when used as veterinary drugs. OSHA has promulgated a final standard of 10 $\mu g/m^3$ for occupational exposure to inorganic arsenic compounds. Additionally, this standard requires personal protective equipment, training, medical surveillance, signs and labeling, and engineering controls. A permissible exposure limit (PEL) of 0.5 mg/m^3 for organic arsenic as an 8-hr TWA also has been adopted by OSHA. NIOSH recommended lowering of the OSHA standard to a 2 $\mu g/m^3$ ceiling sampled over 15 minutes, based on evidence of carcinogenicity in humans. OSHA regulates arsenic and certain arsenic compounds under the Hazard Communication Standard and as chemical hazards in laboratories.

ASBESTOS
CAS No. 1332-21-4

CARCINOGENICITY

There is sufficient evidence for the carcinogenicity of asbestos and the following forms of commercial asbestos in experimental animals: chrysotile (12001-29-5), amosite (12172-73-5), anthophyllite (17068-78-9), and crocidolite (12001-28-4) (IARC V.2, 1973; IARC V.14, 1977; IARC S.1, 1979; IARC S.4, 1982; IARC S.7, 1987). When administered by inhalation, chrysotile, crocidolite, amosite, and anthophyllite induced mesotheliomas and lung carcinomas in rats and mesotheliomas after intrapleural administration. Chrysotile, crocidolite, amosite, and anthophyllite induced mesotheliomas in hamsters after intrapleural administration.